REMARKS

The Office Action of October 24, 2000 presents the examination of claims 17-37. Claims 17-19 are canceled. No new matter is inserted into the application.

Request for Personal Interview

If for some reason this Reply does not place the present application into a condition for allowance, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) prior to the issuance of an Advisory Action to schedule a personal interview.

Rejection under 35 U.S.C. § 103

Claims 17-25 and 27-29 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Dower '603 (USP 5,639,603) in view of Koster '031 (USP 6,043,031). Claims 17-30 are rejected for allegedly being unpatentable over Dower '603 in view of Koster '031, and further in view of Dodge '117 (USP 5,912,117). Finally, claims 17-37 are rejected for allegedly being unpatentable over Dower '603 in view of Koster '031, further in view of Dodge '117, and further in view of the Stratagene Catalogue (1998).

Claims 17-19 are canceled thus rendering rejection of said claims moot. Applicants respectfully traverse the rejection

applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The Present Invention

The present invention is directed to a method for selectively amplifying a DNA corresponding to RNA even in the presence of an admixture of both DNA and cDNA. This method comprises the steps of providing a template cDNA comprising a nucleotide analog and amplifying a desired DNA from the template cDNA in the presence of two or more kinds of nucleotide analogs. At least one nucleotide analog is incorporated in the amplifying step in place of dGTP or dCTP, and at least one nucleotide analog is incorporated in the amplifying step in place of dATP or dTTP. The nucleotide analogs are incorporated into the synthesized chain at a uniform frequency without being affected by the GC content of the template. Therefore, the present invention provides an easy method for selectively amplifying a DNA corresponding to RNA.

Distinctions between the cited prior art references and the present invention

Dower '603 and Koster '031

The Examiner asserts that one skilled in the art would be motivated to combine the teachings of Dower '603 and Koster '031 to achieve the present invention. Applicants respectfully disagree with the Examiner's assertions. There is simply no motivation to one skilled in the art to combine Dower '603 and Koster '031. Further, review of the cited references finds that even the hypothetical combination of the cited references fails to support each and every claimed feature of the present invention. As such, the present invention is not *prima facie* obvious over Dower '603 in view of Koster '031.

First, there is no motivation to the skilled artisan to combine the disclosures of Dower '603 and Koster '031 to achieve the present invention. An object of the present invention is to provide a DNA amplification method capable of selectively obtaining only a DNA fragment having the nucleotide sequence corresponding to RNA even in an admixture of DNA and cDNA. This object of the present invention is achieved through the incorporation of nucleotide analogs (i) and (ii) [(i) being at least one nucleotide analog incorporated in the place of dGTP or dCTP and (ii) being at least one nucleotide analog incorporated in the place of dATP or dTTP] in DNA amplification. This feature of the present invention is recited in the instant claim 20. The nucleotide analogs are incorporated into the synthesized

chain at a uniform frequency without being affected by the GC content of the template.

In contrast, the object of Dower '603 is to facilitate identification of compounds with desired properties from compound collections. Although Dower '603 discloses the incorporation of identifiable oligonucleotide tags in compound collections, Dower '603 fails to disclose a method for amplifying DNA in the presence of two or more kinds of nucleotide analogs. In addition, the oligonucleotide tag utilized by Dower '603 is synthesized by the use of 7-deaza-2'-deoxyadenosine in the place of dA in the template, in order to prevent the acid-catalyzed hydrolysis of the template (see column 27, lines 12 to 30). Further, Dower '603 is silent on the teaching that nucleotide analogs are used during amplification in order to achieve uniform incorporation of the nucleotide analogs into target nucleic acids without the influence of the GC content of the target RNA.

Further, the object of Koster '031 is to provide a fast and accurate mass spectrometer-based process for detecting a particular nucleic acid sequence in a biological sample. As disclosed in Example 8 of Koster '031, PCR products containing 7-deazapurine moieties are used as the sample to be detected. The PCR products are prepared by PCR amplification using 7-deaza-dATP and 7-deaza-dGTP in place of dATP and dGTP,

respectively. Koster '031 fails to disclose that when two or more kinds of nucleotide analogs are used during amplification, a uniform incorporation of these nucleotide analogs into the targeted nucleic acids can be achieved without being affected by the GC content of the target RNA.

In the present invention, however, nucleotide analogs are incorporated into the synthesized chain at a uniform frequency without being affected by the GC content of the template. Therefore, it is easy to set the conditions for selective amplification of a product corresponding to RNA. Because the present invention does not require a step of acid treatment in the preparation of libraries as disclosed by Dower '603, and is not used to prepare a sample for mass spectrometric detection of nucleic acids as disclosed by Koster '031, an ordinary artisan would not be motivated to combine Dower '603 and Koster '031.

Nevertheless, even if Dower '603 and Koster '031 were hypothetically combined, the combination still fails to support each and every element of the present invention. Specifically, neither reference teaches amplification of a nucleotide template containing nucleotide analogs in the presence of nucleotide analogs, for the purpose of selectively amplifying a product corresponding to RNA. Even if the two references were combined, the skilled artisan would merely achieve a method for synthesizing a nucleic acid containing 7-deaza-dATP and 7-deaza-

dGTP, without acid hydrolysis of the nucleic acids usable for evaluation of the mass spectrometric detection of nucleic acids.

Therefore, it would not be obvious to the skilled artisan that a desired DNA can be amplified by using a DNA template comprising nucleotide analogs in the presence of (i) at least one nucleotide analog to be incorporation in place of dGTP or dCTP, and (ii) at least one nucleotide analog to be incorporated in place of dATP or dTTP, simply from the teachings of Dower '603 and Koster '031.

Dodge '117 and the Stratagene Catalogue

The disclosure of Dodge '117 is relied upon by the Examiner to teach the lowering of T_m value with DMSO, while the Stratagene catalog is cited merely to provide motivation for a kit. Applicants respectfully disagree with the Examiner's assertions.

Dodge '117 discloses amplification by PCR, wherein glycerol and other related solvents are used to increase the sensitivity of the PCR during amplification and to overcome problems pertaining to the sequencing of regions of DNA having strong secondary structure. However, Dodge '117 fails to disclose a targeted sequence derived from an RNA can be selectively amplified by the use of glycerol and other related solvents, such as DMSO. As such, the ordinary artisan would not be motivated to combine the inventions of Dower '603, Koster '031,

and Dodge '117 to achieve the instant method of selective DNA amplification. Finally, the Stratagene catalogue fails to cure the deficiencies of Dower '603, Koster '031, and Dodge '117. The Stratagene catalogue merely advertises kits, and does not provide motivation for the instant method of selective DNA amplification.

In conclusion, the Examiner fails to make a *prima facie* case of obviousness. The hypothetical combination of Dower '603 and Koster '031, and further, Dodge '117 and the Stratagene catalogue, still fails to support all of the claimed features of the present invention. Specifically, none of the cited reference teaches amplification of a cDNA template containing nucleotide analogs in the presence of nucleotide analogs.

In sum, all of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Early and favorable action on the merits of the present application is thereby requested.

Pursuant to the provisions of 37 C.F.R. § 1.17 and 1.136(a), Applicants hereby petition for an extension of one (1) month to February 26, 2001 for the period in which to file a response to the outstanding Office Action. The required fee of $110.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or

credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly, extension of time fees.

Respectfully submitted,

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